## REMARKS

Applicant gratefully acknowledges withdrawal of objections to specification and claims and indication that the application is now in compliance with the sequences rules. The claims have been amended to address the remaining rejection of the claims as obvious which is discussed below.

With this amendment, claim 18 has been amended to specify that the probe has a 3' cytosine which is labeled. Support is found in Figure 5, for example. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

**Rejection under 35 U.S.C. § 103(a)**

Claims 18-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Critchley (WO 02/072875) and Buck (1999) as evidenced by Froguel, et al. (1993) and by Howell, et al. (1999).

Applicant request reconsideration in view of amendment of claim 18 to specify "a nucleic acid probe having a 3' terminal cytosine labeled with a fluorescent dye" and arguments presented below.

The Office Action states that the feature of a probe with an end-labeled cytosine is not recited in the rejected claims (Office Action, page 3, last paragraph) and that Critchley teaches probes ending in cytosine.

In response, claim 18 has been amended to specify that the 3' terminal cytosine is labeled. Claim 18 also recites that "the nucleic acid probe has the nucleotide sequence of SEQ ID NO: 21 or 22". Although the Office Action points to 4 sequences in the sequence listing of Critchley that end in cytosine, none of these 4 sequences have any homology to either SEQ ID NOS: 21 or 22. Accordingly, the sequences of Critchley do not meet the claim limitations as amended.

The Office Action also states that there is no support in the specification for one of ordinary skill in the art to recognize that position 230 is important in probe design. In response, the Examiner's attention is directed to the Abstract and claims 7, 15, 16, and 22 as originally

filed. Further support is found in the present specification at pages 5-6, item 7, reproduced below (emphasis added):

> ...or a nucleic acid probe of which 3' end is labeled with a fluorescent dye, in which fluorescence of the fluorescent dye decreases upon hybridization, and which has a nucleotide sequence complementary to a nucleotide sequence starting from the nucleotide number ***230*** in the nucleotide sequence of SEQ ID NO: 2 and having a length of 14 to 40 nucleotides, and fluorescence of the fluorescent dye is measured.

Similar disclosure is found at page 7, item 15; page 8, item 22; page 14, line 9; page 19, lines 12 and 20; and page 23, line 6. Contrary to the statement of the Examiner, the present specification is replete with specific reference to a probe starting from position 230[1].

The Examiner states further that Critchley teaches probe optimization, particularly at page 14, last paragraph. However, the section referred to by the Examiner discusses the importance of probe length, that the probe may be from 8 to 500 base pairs in length and that optimization is "based on the better base pair mismatch discrimination of shorter probes and the better duplex stability of longer probes". Although Critchley teaches optimization of probe length, Critchley is silent regarding the position of the label, more specifically the position of the label at a 3' cytosine in order to detect the mutation at position 3243 of mitochondrial DNA.

Similarly, Howell, et al. teach that designing DASH probes requires selection of "15-21 long nucleotide allelic sequences centered on the polymorphic nucleotide" (see page 88, col. 1-2, bridging paragraph). Likewise, Howell, et al. are silent on optimization by position of the label at a 3' cytosine. Accordingly, neither Critchley nor Howell, et al. teach the importance of the 230 position, and label at a 3' cytosine for detection of the mutation at position 3243 of mitochondrial DNA.

Accordingly, none of the cited references suggests a method for detecting the mitochondrial DNA 3243 mutation by using a nucleic acid probe having a nucleotide sequence

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[1] Note that although claim 18 does not specifically recite "a nucleotide sequence starting from nucleotide number 230 in the nucleotide sequence of SEQ ID NO: 2 and having a length of 14 to 40 nucleotides", claim 18 originally referred to claim 16 which contains this language. In response to the species election of SEQ ID NOS: 20 and 21, claim 18 was amended to recite

complementary to a nucleotide sequence starting from the nucleotide position 230 in the nucleotide sequence of SEQ ID NO: 2, where the 3' end of the probe is a cytosine corresponding to nucleotide position 230 and labeled with a fluorescent dye.

Among many possible probes for detection of the mitochondrial DNA 3243 mutation, Applicant has discovered that a nucleic acid probe with the 3' end as cytosine corresponding to position 230 as shown in SEQ ID NO: 2 is important. Specifically, as shown in Figure 5, the probes of the present invention (i.e., SEQ ID NOS: 21 and 22) were able to detect the mitochondrial DNA 3243 mutation, while other probes could not (Figure 4). The specification describes that only when the probes 3T-mt-R2-18, 3T-mt-R2-17, 3FL-mt-R2-18 and 3FL-mt-R2-17 (probes corresponding to SEQ ID NOS: 21 and 22, see Table 9) were used, changes in fluorescence intensity that could be analyzed by Tm analysis were observed (present specification, page 29, lines 2-5).

One of ordinary skill in the art would not have recognized the importance that the 3' end of the probe should be a cytosine corresponding to nucleotide position 230 of SEQ ID NO: 2, based on the cited references which do not specify SEQ ID NOS: 21 and 22 and discuss optimization in terms of optimization of probe length and position of the polymorphic nucleotide, not with regards to a specific nucleotide at the end point of the probe.

In view of Applicant's amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

**No Disclaimers or Disavowals**

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior

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these sequences which inherently include this feature (see claim objection on page 3 of paper no. 20071017).

prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

**CONCLUSION**

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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